Impairments in multibacillary leprosy; a study from Brazil

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Accepted for publication 16 February 2004

Summary This is a retrospective cohort study of 103 multibacillary leprosy patients (18% BB, 48% BL and 34% LL) followed during and after treatment, in a tertiary referral centre with an outpatient clinic in an endemic area in Brazil, for an average period of 65 months since the start of multidrug therapy (24-dose MDT). The objective of the study was to identify the role of overt neuritis (presence of pain in a peripheral nerve trunk, with or without enlargement or neural function damage), in the development of impairments. They were evaluated using the World Health Organization disability grade before treatment, at the end of the treatment, and at the end of the follow-up period. Thirty-four percent of patients presented overt neuritis during MDT, and 45% had overt neuritis episodes during the follow-up period; the most commonly affected nerves were ulnar, fibular and posterior tibial nerves, and the neuritic episodes were carefully treated with steroid therapy and physiotherapy. Impairments were associated with: affected (painful and/or thick) nerves at diagnosis ($P<0.005$); delay in diagnosis ($P=0.01$); impairments already present at the start of treatment ($P=0.00041$ at the end of MDT, and $P=0.00013$ at the end of follow-up); occurrence of overt neuritis episodes during MDT ($P=0.0016$) or the whole follow-up ($P=0.015$). These data draw attention to the importance of early diagnosis and of good neurological examination throughout the follow-up, as well as suggest the importance of neuritis in the induction of impairments in multibacillary leprosy.

Introduction

The main problem with leprosy is the development of impairments. The neurological sequelae are responsible for the stigma of leprosy as being a deforming disease.\textsuperscript{1–3} To the lay person, leprosy is synonymous with impairments.\textsuperscript{2}

Several factors have been associated with disabilities in leprosy. Multibacillary patients are at higher risk of neural function impairment than paucibacillary ones.\textsuperscript{4–9} Male gender is commonly associated with impairments.\textsuperscript{6,7,10} Delay in diagnosis has been identified in many studies as a risk factor to disabilities already present at the diagnosis.\textsuperscript{4,6,11–18} Older age is
another important risk factor, and some studies have also identified as potential risk factors the extent of clinical disease, the presence of thickened nerves at diagnosis, disabilities already present at the initial examination, and chronic or recurrent neuropathy.

Impairments in leprosy are usually evaluated through the disability grade, as recommended by the World Health Organization. Disabilities are noted in a formulary, and graded in a way of crescent compromise due to leprosy.

Neuritis is considered an important factor in the induction of impairments in leprosy. Overt neuritis is defined as the presence of pain, spontaneous or at palpation, in a peripheral nerve trunk, with or without nerve enlargement or function compromise.

We aimed to study a cohort of multibacillary leprosy patients, in order to identify possible risk factors to the development of impairments associated with the disease, particularly the role of overt neuritis episodes in the induction of them as measured through the WHO disability grade.

Materials and methods

We studied 103 patients, sequentially admitted for 24-dose MDT treatment at Souza Araujo Outpatient Clinic, Oswaldo Cruz Foundation, Rio de Janeiro, Brazil, between January 1990 and December 1992. This is a tertiary referral centre with an outpatient clinic located in a highly endemic area of the country. The individuals were informed about the use of their medical registers and examinations in scientific research, and signed a consent form. We excluded from the study individuals previously submitted to any kind of treatment to leprosy; those who abandoned treatment before its conclusion; and those with neural impairments only, without cutaneous lesions. During this period, 168 multibacillary patients were admitted to treatment at this institution, and 65 were excluded from the study, for the reasons mentioned.

All individuals were submitted to dermato-neurological examination at the moment of the diagnosis. They were treated with 24-dose multidrug therapy, as recommended by the National Health Ministry at the time, being examined monthly during the treatment, and annually after the completion of MDT, or at any time when reactions occurred. The mean period of follow-up of the patients was 64.6 months from diagnosis (median 64.5 months), ranging from 28 to 90 months.

The impairment status was evaluated through the WHO disability grade, calculated at the initial examination, at the end of the treatment, and annually after the completion of MDT. Eyes, hands and feet were examined using Semmes–Weinstein monofilaments sensory test, voluntary muscle test (VMT), and dental thread for the sensory examination of the eyes. Impairments were noted in a proper form, and the grade was as follows: grade 0 = no disability due to leprosy, grade 1 = sensory impairment only, and grade 2 = motor dysfunctions and sequelae due to leprosy. In order to evaluate the relative risks associated with the studied risk factors, we grouped disability grade in ‘no impairments’ and ‘with impairments’, the last category combining grades 1 and 2.

At diagnosis, affected peripheral nerves (thickened and/or painful) were noted, the auricular, supra-orbicular, ulnar, median, radial, fibular, posterior tibial and sural nerves being examined. These trunk nerves were also assessed during subsequent patient observations.
During follow-up, the overt neuritis episodes were carefully noted, and the affected patients were treated with steroids (usually standard treatment with prednisone 1 mg/kg per day, with tapered over 4–5 months), and adequate physiotherapy.

Statistical procedures were performed, and we used Chi-square, Kruskal–Wallis (equivalent to Chi-square) tests, when appropriate.

Results

A total of 103 patients were included in the study.

Affected nerves (thick and/or painful) at diagnosis

Thirty-four patients (33%) did not have affected peripheral nerve trunks at the initial examination, and 69 (67%) presented with nerve involvement (Table 1).

Disability grade before treatment

Forty-five patients had no impairments at diagnosis; 58 had some impairment (35 had disability grade 1; and 23 had disability grade 2).

Disability grade at the end of treatment

Disability grade at the end of treatment was assessed for 102 patients. Sixty-three individuals had no impairment at the end of 24-dose MDT; 40 had some impairment (19 had disability grade 1; and 21 had disability grade 2).

Final disability grade

At the end of follow-up, 65 patients had no impairments; and 38 had some impairment (disability grade 1 in 17, and disability grade 2 in 21). The distribution of impairments at diagnosis, at the end of treatment and at the end of follow-up is shown in Figure 1.

Table 1. Affected nerves (thick and/or painful) at diagnosis and during overt neuritis episodes (painful nerve trunks) during follow-up

<table>
<thead>
<tr>
<th>Peripheral nerves</th>
<th>Affected nerves at diagnosis</th>
<th>Neuritis in follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulnar</td>
<td>53</td>
<td>34</td>
</tr>
<tr>
<td>Tibial posterior</td>
<td>33</td>
<td>22</td>
</tr>
<tr>
<td>Fibular</td>
<td>30</td>
<td>26</td>
</tr>
<tr>
<td>Auricular</td>
<td>29</td>
<td>5</td>
</tr>
<tr>
<td>Radial</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td>Supra-orbicular</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Median</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>Cutaneous radial</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Sural</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Facial</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Cutaneous femoral</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>
Figure 1. Distribution of disabilities according to WHO grading. I: disability grade before treatment. II: disability grade at the end of treatment. III: disability grade at the end of follow-up, final disability grade.

Occurrence of overt neuritis

Thirty-five patients (34%) presented with overt neuritis during 24-dose MDT. Forty-six patients (45%) had overt neuritis during follow-up. The nerve trunks affected were ulnar (34 patients), fibular (26 patients) and posterior tibial (22 patients) (Table 1). The number of episodes of overt neuritis for each affected patient varied from one to seven during treatment, and from one to 17 episodes during the whole study period. Most affected patients had more than one episode during follow-up.

The distribution of overt neuritis episodes along the years since the start of MDT is shown in Figure 2. The incidence of overt neuritis episodes per 100 person-years at risk (PYAR) is shown in Figure 3.
Gender and impairments

In this cohort, 25 individuals (24%) were women, and 78 (76%) were men. There was no significant association between gender and impairments (data not shown).

Age and impairments

Age was inversely associated with impairments at diagnosis ($P = 0.022$), at the end of treatment ($P = 0.00081$) and at the end of follow-up ($P = 0.0010$) (Table 2). When ages were grouped as 0–14 years (one patient), 15–49 years (68 patients) and more than 50 years (34 patients), age was inversely significantly associated with impairments at diagnosis ($P = 0.020$); with impairments at the end of treatment ($P = 0.0092$); and with impairments at the end of follow-up ($P = 0.0066$).

When disability grades were grouped as ‘no impairments’ and ‘with impairments’, age was not associated with impairments at the start of MDT, at the end of treatment or at the end of follow-up ($P > 0.05$) (data not shown).
Table 2. Risk factors for impairments in 103 multibacillary leprosy patients. NS = not significant (P<0.05); CI = 95% confidence interval; MA = median age (years); R & J = Ridley and Jopling classification system; ENL = erythema nodosum leprosum; * 100 patients; 102 patients; K-W = Kruskall–Wallis test; DGET = disability grade at the end of treatment; FDG = final disability grade (end of follow-up)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Level</th>
<th>No. of patients</th>
<th>Relative risk</th>
<th>Impairments at diagnosis</th>
<th>End of 24-dose MDT&lt;sup&gt;a&lt;/sup&gt;</th>
<th>End of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td>Inverse, P&lt;0.022 (K-W)</td>
<td>Inverse, P&lt;0.00051 (K-W)</td>
<td>Inverse, P&lt;0.0010 (K-W)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MA for no impairments = 44</td>
<td>MA for no impairments = 38</td>
<td>MA for impairments = 41</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MA for impairments = 38-5</td>
<td>MA for impairments = 42</td>
<td>MA for impairments = 35</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>78 (76%)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>25 (24%)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Classification (R &amp; J)</td>
<td>BB</td>
<td>19 (18%)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>BL</td>
<td>49 (48%)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>LL</td>
<td>35 (34%)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Delay in diagnosis</td>
<td></td>
<td></td>
<td></td>
<td>P&lt;0.010 (K-W)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Painful/thickened nerves at diagnosis</td>
<td></td>
<td></td>
<td></td>
<td>P&lt;0.005 (Chi²)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Impairments at diagnosis×DGET</td>
<td>Yes</td>
<td>57 (55%)</td>
<td>1.75 (CI: 1.27–2.40)</td>
<td>P&lt;0.00041 (Chi²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impairments at diagnosis×FDG</td>
<td>Yes</td>
<td>57 (55%)</td>
<td>1.93 (CI: 1.42–2.63)</td>
<td>P&lt;0.000013 (Chi²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reaction during treatment</td>
<td>Reversal reaction</td>
<td>33 (32%)</td>
<td>NS</td>
<td></td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ENL</td>
<td>38 (37%)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Overt neuritis during treatment</td>
<td>Yes</td>
<td>35 (34%)</td>
<td>1.76 (CI: 1.22–2.53)</td>
<td>P&lt;0.0016 (Chi²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overt neuritis during follow-up</td>
<td>Yes</td>
<td>46 (45%)</td>
<td>1.80 (CI: 1.14–2.82)</td>
<td>P&lt;0.0015 (Chi²)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Classification and impairments**

Classification according to the Ridley and Jopling system (BB, BL, LL) was not associated with the development of impairments (data not shown). The classification was not associated with the occurrence of overt neuritis episodes during the follow-up period.

**Delay in diagnosis and impairments**

The period of time between the onset of symptoms and diagnosis was reported by patient recall for 100 patients. Twenty-nine individuals had the disease up to 6 months, and 71 people for 7 months or more. The delay in presentation was associated significantly with impairments at diagnosis ($P = 0.010$), but not with impairments during follow-up ($P > 0.05$, data not shown).

**Nerves affected at diagnosis and impairments**

Nerves affected at the initial examination were significantly associated with impairments at the start of treatment ($P < 0.005$), and also with the subsequent occurrence of overt neuritis during the follow-up ($P < 0.05$, Chi-square test).

**Association of impairments at diagnosis with impairments at end of treatment, and at end of follow-up**

Impairments at diagnosis were significantly associated with impairments at the end of treatment ($P = 0.00041$, Chi-square test; $P = 0.000001$, Kruskal–Wallis test). They were also significantly associated with impairments at the end of follow-up ($P = 0.000013$, Chi-square test; $P = 0.000001$, Kruskal–Wallis test).

When disabilities were grouped into ‘no impairments’ and ‘with impairments’, we found that the patients with impairments at diagnosis had 1.75 times increased risk of having impairments at the end of treatment [relative risk (RR) = 1.75; 95% confidence limits for RR: 1.27–2.41]; and patients with impairments at diagnosis had 1.93 times increased risk for impairments at the end of the follow-up period (RR = 1.93; 95% confidence limits for RR: 1.42–2.63).

**Type of reactions and overt neuritis**

Thirty-three patients (32%) presented with reversal reaction episodes during treatment, and 38 (37%) presented with erythema nodosum leprosum (ENL). Overt neuritis episodes were associated with ENL, more than with reversal reactions, but this was not statistically significant ($P > 0.05$, data not shown).

**Overt neuritis and impairments**

Occurrence of overt neuritis episodes during MDT was significantly associated with impairments at the end of treatment ($P = 0.0016$); and during follow-up ($P = 0.015$).

When disability grades were grouped into ‘no impairments’ and ‘with impairments’, we observed that patients with neuritis during MDT had a 1.76 times increased risk of having
impairments at the end of treatment (RR = 1.76; 95% confidence limits for RR: 1.22–2.53), and those with neuritis during accompaniment period had 1.80 times increased risk of impairments at the end of follow-up (RR = 1.80; 95% confidence limits for RR: 1.14–2.82).

**Silent neuropathy**

In this cohort, five patients (4.9%) experienced worsening of their impairment status without overt neuritis (without pain in peripheral nerves), which was detected during routine examination.

**Discussion**

Multibacillary (MB) leprosy patients are more susceptible than paucibacillary (PB) ones to neural function impairment (NFI).4–9 We decided to study retrospectively an MB cohort in a highly endemic area, in order to evaluate the role of overt neuritis in the induction of impairments measured through WHO disability grading. Other factors that could be associated with the outcome, according to the literature (classification according to Ridley and Jopling system, male gender, delay in presentation, age, affected nerves at diagnosis and disabilities already present at the initial examination), were also studied, so we could identify patients at risk of developing NFI.

Classification according to Ridley and Jopling (BB, BL or LL) was not associated with the outcome. Multibacillary patients were thus studied as a group. There was a high percentage (67%) of multibacillary patients with pain and/or thickness of peripheral nerve trunks at the time of diagnosis, and this is a reflection of the delay in presentation. There was also a high percentage of people with impairments at diagnosis (disability grade 1 or 2 in 56%). However, by observing Figure 1, we can see the good influence that MDT treatment has on the patients’ prognosis: there was a decline in the impairments at the end of treatment and at the end of follow-up, in comparison with those before treatment.

Figure 2 shows the occurrence of overt neuritis episodes from the start of MDT, and in Figure 3 the incidence of neuritis episodes per 100 person-years at risk (PYAR) in this cohort. Multibacillary patients present overt neuritis mainly during the second year after the beginning of MDT, followed by a steady decline, so that overt neuritis is rare after 5 years. This is consistent with the previous findings of Saunderson.15 Nowadays, recommended MDT in Brazil is 12 doses, and not 24; most multibacillary patients will present with neuritis after their release from MDT treatment. Patients have to be advised at the end of treatment to return to the basic health unit if they develop pain in peripheral nerve trunks.

Gender (female or male) was not associated with impairments, before, at the end of MDT, or at the end of follow-up, although male gender is frequently found to be a risk factor for NFI.6–8,10

Longer delay in diagnosis was significantly associated with impairments before treatment. Only 29 individuals in this cohort were diagnosed within 6 months. Neural lesions are considered recent when up to 6 months,4 and can be treated with steroid therapy in many cases. NFI of more than 6 months is considered to be difficult to treat.15 Greater delay in diagnosis implies greater severity in neural lesions.20 Early diagnosis of leprosy can prevent NFI in large proportion of patients,4 and is considered very important in the prevention of impairments among leprosy sufferers.6,11,13,14,16,18
Older age is generally considered to be associated with NFI, but we did not find this in our study. In fact, age was closely associated with impairments. These data may result from the institution being a third referral centre, with few young patients. The number of patients between 15 and 49 years of age (n = 68) was twice the number of those above 50 years of age (n = 34), and this is a reflection of age structure of the population.

The presence of thickened and/or painful peripheral nerves at the initial examination had a negative impact on the impairments already present at diagnosis, and was also significantly associated with the occurrence of overt neuritis during follow-up, as noted by other authors. We would like to emphasize the importance of a good neurological examination at diagnosis and subsequently, in particularly the examination of ulnar, fibular and posterior tibial nerves, the most frequently affected with overt neuritis (Table 1). However, in another study, De Rijk et al. did not find a relationship between the presence of impairments at diagnosis and the occurrence of subsequent reactional states among MB patients.

The disability grade before diagnosis was correlated with WHO grading at the end of MDT and at the end of the following period, with a worse prognosis in those with impairments already present at the initial examination. Similar data were found by many other authors.

The occurrence of overt neuritis was a significant risk factor for a poor outcome, during MDT or at the end of follow-up. Neuritis is related to disabilities in leprosy; it is important to recognize its early signs to provide prompt treatment to prevent further sequelae.

In this cohort, 4.9% of individuals experienced worsening of their disability status without pain in peripheral nerve trunks (silent neuropathy, discovered during routine examinations). This is consistent with other studies on silent neuropathy, and shows the necessity of routine neurological examinations of multibacillary leprosy patients.

We must be aware of the potential leprosy patients at risk of developing impairments: multibacillary, with delay in presentation, with painful/thick peripheral nerve trunks and/or with disabilities already present at diagnosis, who develop neuritis during follow-up. (Male gender and older ages are also risk factors in other studies, although not in this one.) These patients must be carefully followed up in order to avoid or reverse leprosy impairments.

References

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